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Catalytic Enantioselective Conjugate Alkynylation of β-Aryl-β-trifluoromethyl Enones Constructing Propargylic All-Carbon Quaternary Stereogenic Centers

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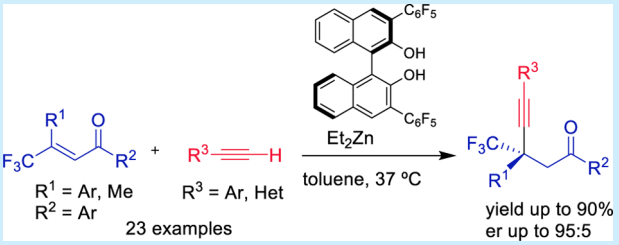
Supporting Information

ABSTRACT: The enantioselective conjugate alkynylation of β-aryl-β-trifluoromethyl enones has been carried out using terminal alkynes and diethylzinc in the presence of 3,3′-bis-(perfluorophenyl)BINOL as the chiral ligand to give the corresponding ketones bearing a trifluoromethylated propargylic quaternary stereocenter with fair to good enantioselectivities. Enones bearing a bulky 2-naphthyl attached to the carbonyl group provided the best enantioselectivities. The synthetic applicability of the resulting products has been demonstrated with their iodocyclization to form 4*H*-pyrans.



Chiral fluorinated compounds have found wide application in different fields, including medicinal,[1] agricultural,[2] and materials sciences.[3] In particular, molecules bearing a chiral center attached to a trifluoromethyl substituent[4] have raised special interest because of the occurrence of this motif in biologically active compounds,[5] chiral reagents,[6] and materials with optoelectronic properties.[7] The trifluoromethyl group has a larger size than the methyl group, and its strong electron-withdrawing nature and high lipophilicity often alter the physical, chemical, and biological properties of the parent molecules.[1−3] Accordingly, considerable efforts have been addressed to the catalytic asymmetric synthesis of molecules with a CF_3-containing stereocenter using either trifluoromethylation of prochiral carbons[8] or functionalization of trifluoromethylated prochiral carbons, i.e., trifluoromethyl ketones,[9] trifluoromethyl imines,[10] or β-trifluoromethyl enones.[11] In this context, the synthesis of all-carbon quaternary stereocenters[12] containing a CF_3 group constitutes an extraordinary challenge for organic synthetic chemists.[13] One way to achieve this goal is the use of electrophilic alkenes as Michael acceptors. After the pioneering work by Shibata on the conjugate addition of cyanide to β-aryl-β-trifluoromethyl enones,[14] several carbon nucleophiles have been reacted with β-aryl-β-trifluoromethyl enones[15] and nitroalkenes[16] in a catalytic enantioselective fashion.

During the last years, the enantioselective conjugate addition of alkynes to unsaturated carbonyl compounds has been developed as a way to construct propargylic stereogenic centers.[17] The resulting compounds are interesting building blocks because of the presence of two functional moieties, i.e., a carbonyl group and a C−C triple bond. Good results in terms of yields and enantioselectivities have been obtained with different catalytic systems for a number of β-monosubstituted carbonyl compounds, including the alkynylation of β-trifluoromethyl enones reported by our group.[17d] Fillion has reported the conjugate alkynylation of alkylidene Meldrum's acids with alkynylalanes and alkynyl Grignards to provide quaternary propargylic stereocenters in a non-enantioselective manner.[18] However, to the best of our knowledge, an enantioselective conjugate alkynylation of β,β-disubstituted enones has not been reported to date. Herein we describe the first example of enantioselective conjugate alkynylation of β-aryl-β-trifluoromethyl enones with terminal alkynes.

To start our research, we studied the reaction between phenylacetylene (**2a**) and (*E*)-enone **1a** under the conditions developed previously by our group for the alkynylation of β-trifluoromethyl enones, which involve the use of Cu(I) salts and biphosphine ligands,[17d−g] but we did not observe any advance of the reaction. Therefore, we moved to a Zn-based catalytic system constituted by binaphthol ligands and diethylzinc in toluene at 70 °C (Scheme 1 and Table 1), which was used by us in the alkynylation of enediones.[17k] From all commercially available BINOL-type ligands, ligand **L4** bearing two 3,5-bis-(trifluoromethyl)phenyl groups at positions 3 and 3′ of the binaphthol system provided the best enantioselectivity (78:22 er; Table 1, entry 4). Since the presence of electron-withdrawing groups at these positions seemed to improve the enantioselectivity, we prepared and tested ligand **L5** bearing two perfluorophenyl groups, which provided **3aa** in 68% yield with 85:15 er (Table 1, entry 5). Other binaphthol and related ligands such as VANOL (**L8**) and VAPOL (**L9**) gave lower results (Table 1, entries 6−9).

To minimize an observed non-enantioselective background reaction (Table 1, entry 10), the temperature was decreased to 37

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Scheme 1. Determination of the Absolute Stereochemistry of Compound 3aa

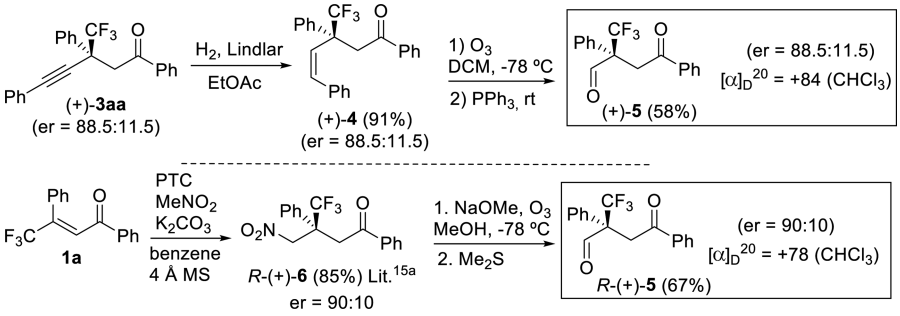
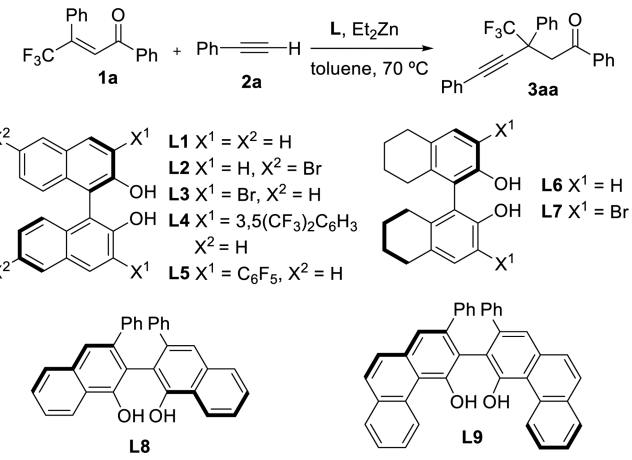


Table 1. Optimization of the Reaction Conditions[a]



entry	L (mol %)	equiv of **2a**	equiv of Et_2Zn	T (°C)	t (h)	yield (%)	er[b]
1	**L1** (20)	7.5	2	70	20	80	70:30
2	**L2** (20)	7.5	2	70	20	–	–
3	**L3** (20)	7.5	2	70	20	29	55:45
4	**L4** (20)	7.5	2	70	20	70	78:22
5	**L5** (20)	7.5	2	70	20	68	85:15
6	**L6** (20)	7.5	2	70	20	–	–
7	**L7** (20)	7.5	2	70	20	50	50:50
8	**L8** (20)	7.5	2	70	20	60	75:25
9	**L9** (20)	7.5	2	70	20	46	50:50
10	–	7.5	2	70	20	50	50:50
11	**L5** (20)	7.5	2	37	30	53	88.5:11.5
12	**L5** (20)	7.5	2	rt	–	–	–
13[c]	**L5** (20)	7.5	2	37	–	–	–
14[d]	**L5** (20)	7.5	2	37	30	35	80:20
15	**L5** (20)	5	2	37	30	40	88.5:11.5
16	**L5** (20)	7.5	1.3	37	30	46	88.5:11.5
17	**L5** (10)	7.5	2	37	30	39	83:17

[a]**1a** (0.125 mmol), **2a**, 1.5 M Et_2Zn in toluene, **L**, toluene (1.5 mL). [b]Determined by HPLC with chiral stationary phases. [c]With $EtNO_2$ as an additive. [d]With CH_2Cl_2 as an additive.

°C, which improved the enantioselectivity to 88.5:15.5 er (Table 1, entry 11); however further decreasing the temperature to rt brought about a complete lack of reactivity. The use of a cosolvent such as nitroethane[17k] or dichloromethane did not improve the results (Table 1, entries 13 and 14). Decreasing the amount of alkyne or diethylzinc did not affect the enantioselectivity, although it was deleterious for the reaction yield (Table 1, entries 15 and 16). Finally, a decrease in the catalyst loading to 10 mol % decreased the enantioselectivity and yield (Table 1, entry 17).

With the best conditions affordable with this catalytic system, we studied the applicability of the reaction (Table 2). A number of 1-phenyl enones **1** (R^2 = Ph) having different aryl substituents on the β-carbon reacted with phenylacetylene to give the expected products **3** in fair to good yields and enantiomeric ratios between 83.5:16.5 and 88.5:11.5 (Table 2, entries 1−5). The use of an E/Z mixture (45:55) of enone **1b** yielded compound **3ba** with 62:38 er, indicating the importance of the double-bond geometry (Table 2, entry 2).[19] The 1- and 3-aryl groups were also amenable to variation. In particular, a bulky 2-naphthyl group attached to the carbonyl moiety provided the highest enantioselectivities (90:10 to 93:7 er) in the addition of phenylacetylene (Table 2, entries 9−12). A methyl group at the β-position (**1l**) was tolerated, although the reaction product was obtained with low er (Table 1, entry 12). On the other hand, no conjugate addition was observed with methyl enone **1m**, which provided the racemic 1,2-addition product (Table 2, entry 13). Although ligand **L5** normally gave the highest enantioselectivity, ligand **L4** provided better results with compounds **3ea** and **3ga** (Table 2, entries 5 and 7) which were obtained in 47% yield (74:26 er) and 45% yield (70:30 er), respectively, with **L5**. The reaction was also tested with substituted phenylacetylenes **2** having electron-donating or electron-withdrawing groups on the phenyl ring (Table 2, entries 14−25) and with 3-ethynylthiophene (Table 2, entries 22 and 23), which performed similar to or better than phenylacetylene, providing the expected alkynylated products with er from 87:13 to 95:5. Unfortunately, neither 4-nitrophenylacetylene (**2f**) nor 4-phenyl-1-butyne (**2g**) reacted under the optimized conditions (Table 2, entries 24 and 25). Finally, it is interesting to note that compounds **3** are prone to crystallize as racemates from hexane/CH_2Cl_2 mixtures, allowing almost enantiomerically pure compounds to be obtained from the crystallization mother liquors (Table 2, entries 7, 17, and 18).

Although racemic compounds **3** could be obtained in crystalline form, highly enantiomerically enriched compounds **3** were obtained as oils, thus hampering the determination of their absolute stereochemistry by X-ray techniques. To determine the absolute stereochemistry of compound (+)-**3aa**, it was transformed into aldehyde **5** in a sequence involving hydrogenation of the triple bond with Lindlar's catalyst followed by ozonolysis of the double bond in compound **4** (Scheme 1). The optical rotation sign and chiral HPLC traces of compound **5** thus obtained coincided with those of the same compound prepared by a Nef-type reaction from the known-stereochemistry compound (*R*)-(+)-**6**, which was synthesized by a modification of Shibata's procedure.[15a] Accordingly, the *R* configuration was assigned to the quaternary stereocenter in compound **3aa** and for the rest of alkynylation products **3** upon the assumption of a uniform stereochemical pathway.

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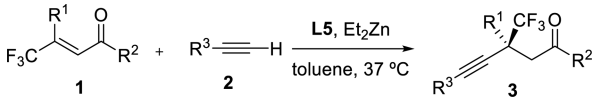
Table 2. Enantioselective Conjugate Alkynylation of β-Aryl-β-trifluoromethyl Enones[a]

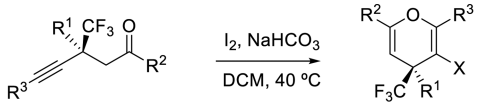


entry	1	R^1	R^2	2	R^3	3	yield (%)	er[b]
1	**a**	C_6H_5	C_6H_5	**a**	C_6H_5	**3aa**	53	88.5:11.5
2	**b**	4-MeC_6H_4	C_6H_5	**a**	C_6H_5	**3ba**	50 (47)[c]	88:12 (62:38)[c]
3	**c**	4-$MeOC_6H_4$	C_6H_5	**a**	C_6H_5	**3ca**	50	87.5:12.5
4	**d**	4-FC_6H_4	C_6H_5	**a**	C_6H_5	**3da**	61	85.5:15.5
5[d]	**e**	4-BrC_6H_4	C_6H_5	**a**	C_6H_5	**3ea**	88	83.5:16.5
6	**f**	C_6H_5	4-$MeOC_6H_4$	**a**	C_6H_5	**3fa**	70	89:11
7[d]	**g**	C_6H_5	4-ClC_6H_4	**a**	C_6H_5	**3ga**	60 (63)[e]	79.5:20.5 (97.5:2.5)[f]
8	**h**	C_6H_5	4-$NO_2C_6H_4$	**a**	C_6H_5	**3ha**	44	83:17
9	**i**	C_6H_5	2-naphthyl	**a**	C_6H_5	**3ia**	50	91.5:8.5
10	**j**	3-MeC_6H_4	2-naphthyl	**a**	C_6H_5	**3ja**	76	93:7
11	**k**	3-$MeOC_6H_4$	2-naphthyl	**a**	C_6H_5	**3ka**	50	90:10
12	**l**	Me	2-naphthyl	**a**	C_6H_5	**3la**	90	71.5:28.5
13	**m**	C_6H_5	Me	**a**	C_6H_5	**3′ma**	55[g]	50:50[g]
14	**a**	C_6H_5	C_6H_5	**b**	4-$MeOC_6H_4$	**3ab**	65	90:10
15	**i**	C_6H_5	2-naphthyl	**b**	4-$MeOC_6H_4$	**3ib**	86	92:8
16	**j**	3-MeC_6H_4	2-naphthyl	**b**	4-$MeOC_6H_4$	**3jb**	72	90:10
17	**a**	C_6H_5	C_6H_5	**c**	3-FC_6H_4	**3ac**	51 (77)[e]	87:13 (98.5:1.5)[f]
18	**a**	C_6H_5	C_6H_5	**d**	4-FC_6H_4	**3ad**	81 (77)[e]	90:10 (99.5:0.5)[f]
19	**i**	C_6H_5	2-naphthyl	**d**	4-FC_6H_4	**3id**	90	95:5
20	**n**	4-MeC_6H_4	2-naphthyl	**d**	4-FC_6H_4	**3nd**	82	94:6
21	**o**	4-$MeOC_6H_4$	2-naphthyl	**d**	4-FC_6H_4	**3od**	66	91.5:8.5
22	**a**	C_6H_5	C_6H_5	**e**	3-thienyl	**3ae**	44	91:9
23	**i**	C_6H_5	2-naphthyl	**e**	3-thienyl	**3ie**	64	93:7
24	**i**	C_6H_5	2-naphthyl	**f**	4-$NO_2C_6H_4$	–	–	–
25	**a**	C_6H_5	C_6H_5	**g**	$PhCH_2CH_2$	–	–	–

[a]**1** (0.125 mmol), **2** (0.94 mmol), 1.5 M Et_2Zn in toluene (0.13 mL, 0.25 mmol), **L5** (0.025 mmol), toluene (1.5 mL), 37 °C, 30 h. [b]Determined by HPLC with chiral stationary phases. [c]The reaction was carried out with an *E*/*Z* mixture (45:55) of enone **1b**. [d]The reaction was carried out at rt with **L4**. [e]The yield of **3** recovered from the crystallization mother liquor (hexane/CH_2Cl_2) is shown in parentheses. [f]The er of **3** recovered from the mother liquor is shown in parentheses. [g]Yield and er of the 1,2-addition product (see the Supporting Information).

To show the potential applicability of compounds **3**, we developed a cyclization reaction promoted by iodine in basic media (Scheme 2).[20] Under these conditions, a number of β-alkynyl enones **3** were converted into the corresponding 3-iodo-4*H*-pyrans **7** bearing a trifluoromethylated quaternary stereocenter in good yields. On the other hand, compound **3ab** having a 4-methoxyphenyl group attached to the triple bond provided deiodinated pyran **8ab** in 90% yield under similar conditions (see Scheme S1).

Scheme 2. Iodine-Promoted Cyclization of Compounds 3 To Form 4*H*-Pyrans 7



3aa, $R^1 = R^2 = Ph$, $R^3 = Ph$
3ad, $R^1 = R^2 = Ph$, $R^3 = 4\text{-}FC_6H_4$
3ae, $R^1 = R^2 = Ph$, R^3 = 3-thienyl
3ba, $R^1 = 4\text{-}MeC_6H_4$, $R^2 = Ph$, $R^3 = Ph$
3ca, $R^1 = 4\text{-}MeOC_6H_4$, $R^2 = Ph$, $R^3 = Ph$
3fa, $R^1 = Ph$, $R^2 = 4\text{-}MeOC_6H_4$, $R^3 = Ph$
3ha, $R^1 = Ph$, R^2 = 2-naphthyl, $R^3 = Ph$
3ab, $R^1 = R^2 = Ph$, $R^3 = 4\text{-}MeOC_6H_4$

7aa, X = I (70%)
7ad, X = I (63%)
7ae, X = I (68%)
7ba, X = I (87%)
7ca, X = I (78%)
7fa, X = I (77%)
7ha, X = I (62%)
8ab, X = H (90%)

In summary, we have described the catalytic enantioselective conjugate alkynylation of β-aryl-β-trifluoromethyl enones[21] using terminal alkynes, diethylzinc, and a BINOL-type ligand. The corresponding ketones bearing a trifluoromethylated propargylic quaternary stereocenter were obtained in fair to good yields and enantioselectivities. Bulky groups attached to the carbonyl moiety improved the enantioselectivity. This is the first catalytic enantioselective conjugate alkynylation of β,β-disubstituted enones reported in the literature. The synthetic applicability of the resulting products has been demonstrated by their cyclization to form 4*H*-pyrans.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01494.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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